*Neuropharmacology* Vol. 23, No. 12B, pp. 1537–1551, 1984
Printed in Great Britain

0028-3908/84 $3.00 + 0.00
Pergamon Press Ltd

# SEROTONIN AND APPETITE

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## 1. GENERAL BACKGROUND TO REVIEW

### *1.1. Introduction*

The proposition that serotonin may be involved in the control of intake of food and the expression of appetite is less than 10 years old. Indeed, in a 600 page anthology of serotonin and behaviour published in 1973 (Barchas and Usdin, 1973) neither feeding behaviour nor food intake were included in the subject index. This late development of the link between serotonin and feeding is surprising. First, serotonin systems occupy a strategic anatomical location, projecting to and coursing through hypothalamic zones (Azmitia, 1978), where they could be expected to contribute to the dramatic changes in food consumption and body weight following experimentally-induced hypothalamic damage. Second, serotonergic neurones are widely distributed in the gut (Gershon and Dreyfus, 1977; Ahlman, 1976; Fozard, 1984) where modifications of gastrointestinal functioning would give rise to repercussions in feeding activity. Although the earliest conceptualisations of neurochemical models of feeding control emphasised noradrenaline (Grossman, 1962; Booth, 1967) or dopamine (Ungerstedt, 1971; Marshall, Richardson and Teitelbaum, 1974), more recently two reviews have been specifically devoted to the role of serotonin (Blundell, 1977, 1979), whilst other reviews have given considerable attention to the issue (Hoebel, 1977; Coscina, 1977; Leibowitz, 1980) or have dealt with specialised aspects (e.g. Garattini, 1978). There is now no doubt that certain experimental manipulations of serotonergic metabolism produce marked effects on food consumption and less potent effects on other aspects of feeding behaviour. Do these results mean that some serotonin-containing neurones play a role in the natural regulatory system which serves to match an organism's nutritional intake to its bodily requirements? The present review will draw together recent research findings and suggest an appropriate interpretation of the data. It should be mentioned immediately that research on serotonin and feeding is progressing only gradually and has not yet been embraced by work on the characterisation of receptor subtypes. There appear to be two reasons for this. First, researchers have been preoccupied with establishing the validity and reliability of the basic relationship between serotonin adjustments and food intake. Second, there has been a concern to verify that any relationship involves a rational link between nutritional factors and neurochemical systems and is not dependent upon the mediation of a third factor such as changes in temperature, arousal or sedation. It is appropriate that a settlement of these methodological issues should precede the investigation of any association between feeding and a particular sub-type.

### *1.2. Summary*

Research over the last 10 years has given rise to a particular pattern of findings and is characterised by certain clear trends. It is appropriate to state these clearly as a basis for the present examination of the field. The most striking and consistent effect is the suppression of food intake by experimental treatments which directly or indirectly activate serotonin receptors. There appears to be no exception (published in the literature) to this general rule. Consequently, activation of serotonin pathways or metabolism is a *sufficient*, though of course not a necessary, condition for the inhibition of food intake in experimental test situations. The converse of this effect, an increase in food intake resulting from an inhibition of serotonin metabolism or a blockade of receptors, is a much weaker phenomenon though it can be detected under suitable experimental circumstances. There are both theoretical and methodological reasons why an increase in food intake is a more elusive phenomenon than an anorexic action (see Blundell, 1981a for a discussion of this issue). One parsimonious interpretation of the effects of serotonin-induced manipulations of food intake is that certain serotonin-containing neurones and pathways mediate in the process of satiation (bringing an eating episode to a halt) and maintain the state of satiety (period of inhibition over further eating).

One further research theme in the field of serotonin and appetite concerns the proposal that serotonin-containing neurones may be involved in the selection of particular nutritional commodities, such as protein or carbohydrate, and in the expression of preferences for these macronutrients. The evidence for this hypothesis arises from experiments on nutritional manipulations and changes in dietary self-selection following experimental interventions in serotonin systems. Considerable methodological and technical

problems confront experimentation on dietary self-selection and nutrient intake (see Blundell, 1983 for review) and it is not surprising that there is disagreement between different research findings.

An important aspect of research on serotonin and feeding is the relative contributions of central and peripheral serotonin stores. In many studies treatments have been used which influence both aspects simultaneously and it appears that changes in feeding can come about after interventions in either the brain or the periphery.

These brief summarising comments have been set down at this stage in order to draw attention to the major issues and to serve as a focus for the review and for the development of future research.

### *1.3. Clinical implications*

At this stage research is still directed toward establishing a functional role of endogenous serotonin systems in the control of food intake. Even if there is not complete unanimity of opinion on this issue certain empirical facts are clear; pharmacological manipulation with serotoninergic drugs gives rise to both dramatic and subtle effects on feeding. Accordingly, such drugs can be used clinically to assist in the management of certain types of feeding disorders. Drugs for the inhibition of eating are used in the management of obesity and may find a use in the treatment of binge eating episodes which represent a major symptom of the condition named bulimia nervosa (Russell, 1979). Drugs which augment eating have been used in the treatment of anorexia nervosa (Benady, 1970), and agents which influence nutrient preferences, such as the desire for protein or carbohydrate, could be used in the treatment of eating disorders displaying particular aberrant patterns of eating. The demand for the development of effective drugs in this area is increasing in view of the prevalence of disorders of feeding and body weight. It is estimated that between one quarter and one third of the adult population of the U.K. may be defined as mildly obese (Garrow, 1982) whilst about 2% of the female population between the ages of 20 and 40 suffer from the eating disorder of bulimia nervosa (Cooper and Fairburn, 1983).

One further clinical implication seems important. A number of classes of psychotropic drugs, such as anxiolytic and antidepressant agents, may influence metabolism of serotonin. Such drugs also may bring about changes in eating and body weight (see Blundell, 1980). This is particularly true of benzodiazepine-type anxiolytics (e.g. Edwards, 1977) which have been characterised as hunger-mimetic agents (Cooper, 1980). It follows that a drug influencing the activity of serotonin systems and administered as treatment for a particular condition may, as a byproduct, bring about changes in appetite, eating and body weight. Consequently, there may be already in existence a sub-class of eating or weight disorders which are drug-induced.

### *1.4. A note on terminology*

In scientific research on the control of feeding, terms such as hunger, appetite, satiation and satiety have specific meanings and refer to particular states or processes (see Blundell, 1979 for discussion and review). In day-to-day discourse however, terms such as hunger and appetite may be used interchangeably as if they were different versions of the same phenomenon. The term appetite used in the title of this chapter simply serves to connote a relationship to events controlling food consumption. In the body of the text however, the meaning of such terms will be more strictly delimited. In the study of food intake there is a clear need to separate the "urge to begin eating" from "the amount consumed"; separate processes control these aspects of feeding. There is also evidence for a disengagement between the willingness to obtain food and the willingness to eat food once it has been obtained. Accordingly, a distinction may be made between hunger, defined as the process which stimulates the onset of eating, and appetite, a process which directs and guides eating once feeding has begun. In turn, satiation can be defined as the "process" which brings eating to a halt whilst satiety is the "state" of inhibition over further eating. Assignation of the term satiation is problematic. Frequently the action of a drug to inhibit food intake is regarded as an action upon the process of satiation. However, satiation can only properly be invoked when the cessation of feeding is due to the consequences of ingestion of food (or to the activation of processes mediating this cessation). The mere observation of reduced intake is obviously insufficient evidence to justify the use of satiation or satiety (Blundell, 1979b; Blundell and Latham, 1979a).

This discussion is not simply about semantic niceties. The distinction between different terms reflects the operation of separate processes underlying the control of feeding behaviour. Food intake is not simply switched on and off; an episode of food consumption represents the end product of an interaction between various distinguishable operations. There is evidence that these operations are influenced by different physiological and neurochemical events. Consequently, in proposing that serotonin influences food intake it is necessary to inquire about the particular operations which may be adjusted by this neurotransmitter. Recognition of this issue has implications for the design and interpretation of experiments.

## 2. METHODOLOGICAL REQUIREMENTS

The investigation of a relationship between a neurotransmitter (serotonin) and behaviour (feeding) demands sophisticated strategies for the manipulation and measurement of serotonin, together with sensitive techniques for measuring and monitoring feeding behaviour. Congruence between the out-

Table 1. Strategies used in investigations of 5-HT and feeding

1. Pharmacological manipulation by peripheral route, administration of agonists, antagonists, releasers, uptake blockers.
2. Administration of 5-HT precursors.
3. Raphe lesions.
4. Use of 5-HT neurotoxins.
5. Central micro-injections.
6. Knife cuts in diencephalon.
7. Experimental and genetic obesity.
8. Starvation and refeeding.

comes of different strategies will strengthen the credibility of any proposed relationship.

### *2.1. Strategies of investigation*

The various experimental strategies used to investigate the relationship between serotonin and feeding are set out in Table 1. The last two procedures have not been widely used and will not be extensively discussed here. The tactic with both experimental and genetic obesity has been to bring about a condition characterised by increases in food intake and fat deposition and to relate these alterations to measured changes in the metabolism of serotonin in brain. For example, it has been reported that ob/ob mice have elevated levels of 5-HT in brain, total tryptophan in plasma and plasma-free tryptophan (Garthwaite, Kahlkoff, Guansing, Hagen and Menahan, 1979) whilst in the fa/fa rats, obese animals showed lower levels of trytophan in several regions of brain but a depressed level of 5-HT only in the mesencephalon (Finkelstein, Chance and Fischer, 1983). These findings are particularly difficult to interpret since it is known that during the course of the development of obesity in genetically-disposed rodents, food intake may be greater than, equal to or less than that of controls, depending on the age of the animal and the "dynamic" or "static" nature of weight gain (Dilettuso and Wangsness, 1977). Accordingly, in the absence of measures of food intake (of obese and lean animals), it is not possible to assess the nature of the relationship between alterations in 5-HT and the tendency to feed. A similar consideration applies to the interpretation of experiments on rats made obese by administration of gold-thio-glucose, where results from different studies have produced inconsistent results (Gal, Morgan and Marshall, 1965; Ishizaki, 1974; Coscina, McArthur, Stancer and Godse, 1978).

The strategy of measuring changes in 5-HT, following food deprivation or re-feeding, does not provide strong evidence for a relationship between brain and behaviour. It has been demonstrated that 24 hr of food deprivation increases the concentration of tryptophan in brain (Curzon, Joseph and Knott, 1972), increases synthesis of 5-HT (Perez-Cruet, Tagliamonte, Tagliamonte and Gessa, 1972) and increases turnover of 5-HT in the lateral hypothalamus (Kantak, Wayner and Stein, 1978). However, in the absence of data on the effects of the treatments on other neurotransmitters known to affect feeding, the changes in metabolism of 5-HT cannot be interpreted unambiguously. Experimental designs in which all amines have been measured, or in which it can be certain that only 5-HT has been manipulated, offer stronger grounds for establishing a relationship between 5-HT and feeding.

### *2.2. Behavioural procedures for the investigation of feeding*

In traditional research on the pharmacology of food intake, procedures have been used which can be administered rapidly and simply. One common technique consists of weighing the food consumed by animals (usually rats) in a discrete test interval (usually 1 or 2 hr) following a lengthy period of food deprivation (e.g. Tedeschi, 1966). Alternatively, animals may be placed on cyclic training programmes when they are obliged to eat at specific times during the day when allowed access to food. The combination of severe food deprivation, a brief test period and a single measure of the weight of food consumed, creates an experimental situation which may be particularly insensitive to certain effects of drugs (for discussion of this issue see Blundell and Latham, 1978, 1979, 1982).

These considerations have prompted the development of more sensitive behavioural assays for feeding, which detect more subtle changes in the disposition of an animal to eat, and which sample a wider range of feeding activities. Central to this issue is the recognition that intake of food is a form of behaviour which is expressed over time and has a particular structure. The observations and analysis of the structure of feeding behaviour not only provides a sensitive technique for detecting mild effects of drugs but also reveals the underlying motivational processes (hunger, satiation etc) which control the disposition to feed. Accordingly, the new procedures used in the behavioural pharmacology of feeding have created a number of modifications to the traditional approach, these include the much finer analysis of the temporal structure of feeding behaviour, the limited use of food deprivation and promotion of the continuous monitoring of eating in free-feeding animals, the presentation of a variety of food items as an alternative to bland laboratory chow, and the use of diets varying in macronutrient content which allow selective ingestion of commodities. These procedures constitute an expansion of the range of feeding situations and may be summarised as follows:

1. Micro-structural analysis of feeding behaviour.
2. Continuous monitoring of behaviour in freely-

feeding animals with the measurement of meal patterns and feeding profiles.

3. Voluntary self-selection of different diets varying in macronutrient content.

4. Presentation of food items characterised by their novelty, variety and palatability.

In certain cases these procedures can be combined to provide a total picture of an animal's feeding repertoire (Fig. 1) and the individual procedures have been fully described elsewhere (Blundell, 1981a, b; Blundell and Latham, 1978, 1982; Blundell and McArthur, 1981). Taken together, a variety of experimental strategies for manipulating or monitoring 5-HT, and sensitive procedures for measuring feeding behaviour, should provide the basis for evaluating the proposition that serotonin is involved in the control of food intake.

## 3. PHARMACOLOGICAL MANIPULATION WITH PERIPHERALLY ADMINISTERED AGENTS

### *3.1. Agonists, releasers and reuptake blockers*

A number of compounds are available whose net effect is to facilitate 5-HT synaptic activity. These compounds include fenfluramine and its derivatives, *m*-chloro-phenyl-piperazine (m-CPP), another piperazine derivative 6-chloro-2(1-piperazinyl)pyrazine (MK-212), indalpine (LM-5008). fluoxetine (Lilly 110140), *dl*-8-chloro-11-anti-amino-benzo(b)bicyclo-[3,31]nona-3, 6a(10a)diene hydrochloride (ORG 6582) femoxatine (FG 4963), zimelidine and quipazine. All of these compounds have been demonstrated to produce an inhibition of food consumption, an effect consistent with the hypothesis that enhancing central serotoninergic transmission causes anorexia. In many aspects fenfluramine is representative of this category of drugs and is distinguished by being widely used in research. Experiments with fenfluramine can be used to exemplify the characteristics of the class though it is not suggested that all produce identical effects.

For fenfluramine, it has been demonstrated that the drug releases serotonin from nerve endings and inhibits reuptake into the neurone (e.g. Garattini and Samanin, 1976). However, it should be considered that the neurochemical effects vary according to whether the parent drug or the main metabolite, norfenfluramine, is given and also depend upon the administration of the *d*- or *l*-isomer. For example, it has been proposed that *d*-fenfluramine and *d*-nonfenfluramine release 5-HT from two different pools (Samanin and Garattini, 1982). This does not appear to be true for the *l*-forms which, in addition, have a weaker action on 5-HT. Consequently, when the racemic form of fenfluramine is administered several different mechanisms may be invoked simultaneously.

Evidence for the involvement of 5-HT in the anorexic action of fenfluramine rests on the capacity of treatments which interfere with synthesis of 5-HT or synaptic transmission to antagonise the drug-induced inhibition of food intake. For example, methysergide, which antagonized the hypothermic effect of fenfluramine in dogs (Jesperson and Scheel-Kruger, 1970) also antagonised the anorexic action of moderate (Blundell, Latham and Leshem, 1973) and large (Barrett and McSharry, 1973) doses of fenfluramine in rats. In addition, other drugs believed to block post-synaptic 5-HT receptors, such as methergoline (Funderburk, Hazelwood, Ruckhart and Ward, 1971; Jesperson and Scheel-Kruger, 1973),

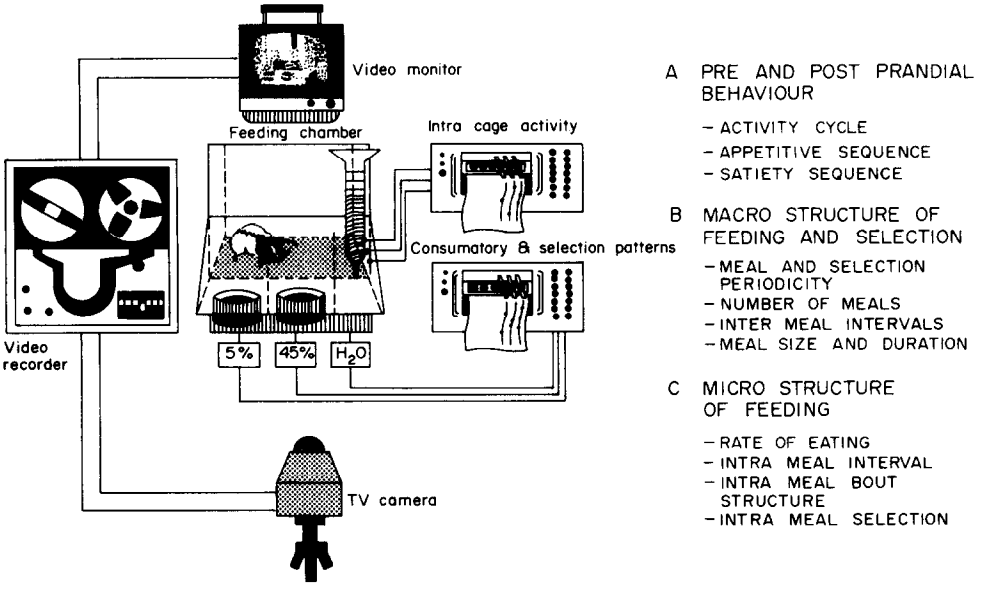


Fig. 1. Plan of the technique for the computer-logged continuous monitoring of diet selection (from 2 diets varying in nutrient composition), meal patterns, locomotor activity and related behaviour.

cinanserin (Clineschmidt, McGuffin and Werner, 1974) and cyproheptadine (Garattini and Samanin, 1976) also partially antagonise the suppressant action of fenfluramine on feeding. It is however possible that these drug interactions could arise through peripheral metabolic effects, resulting in a reduced level of fenfluramine in blood (and brain).

Pretreatment of rats with intraventricular injections of 5,6-dihydroxytryptamine, which is neurotoxic for central 5-HT-containing neurones (Nobin and Bjorklund, 1978) attenuated the anorexic effect of fenfluramine (Clineschmidt, 1973), though contradictory results have been obtained (e.g. Hollister, Ervin, Cooper and Breese, 1975). However, the most striking reduction of the anorexic effect of fenfluramine has been achieved following electrolytic lesions of the median raphe nuclei (Samanin, Ghezzi, Valzelli and Garattini, 1972), though it should be noted that other studies have shown lesser effects (Fuxe, Farnebo, Hamberger and Ogren, 1975) or no effect (Sugrue, Goodlet and McIndewar, 1975) of this procedure. Indeed, it now seems likely that a number of experimental parameters may influence the relationship between anorexia induced by fenfluramine and the integrity of central serotonin systems, for two further studies have reported little or no effect on the action of fenfluramine, following raphe lesions (Carey, 1976) or depletion of 5-HT by intraventricular injection of 5,7-dihydroxytryptamine (Hoebel, Zemlan, Trulson, Mackenzie, Ducret and Norelli, 1978). Moreover, at least two experimental reports have observed a paradoxical enhancement of anorexia induced by fenfluramine following central manipulations of 5-HT. These findings suggest a need for close scrutiny of important experimental variables, including the regime used for the measurement of food intake, the extent and location of central depletion of 5-HT, and the time interval between treatment and testing of the anorexic drug.

One further approach to the understanding of the action of fenfluramine has been through the comparison of the mechanisms underlying the suppressant effects of amphetamine and fenfluramine on feeding. One powerful procedure has been the use of these compounds as a drug-pair in double-dissociation designs (e.g. Blundell, Latham, McArthur, Moniz and Rogers, 1979). It has typically been demonstrated that procedures which ameliorate anorexia produced by amphetamine have little effect on fenfluramine or even lead to an enhancement of its suppressant action. For example, lesions of the lateral hypothalamus (Blundell and Leshem, 1974), intraventricular injections of 6-hydroxydopamine and tranylcypromine (Fibiger, Zis and McGeer, 1973), or lesions of the dopamine-containing nigro-striatal tract (Carey and Goodall, 1975), all reduce the anorexic effect of amphetamine but fail to ameliorate the effect of fenfluramine. The anorexic action of the two drugs can also be dissociated after intrahypothalamic injection (Blundell and Leshem, 1973) and after lesions of the ventral noradrenergic bundle (Garattini and Samanin, 1976), which augment anorexia produced by fenfluramine (Ahlskog, Randall, Hernandez and Hoebel, 1984) in a similar manner to lateral hypothalamic lesions (Blundell and Leshem, 1974). Consequently, while noradrenaline systems (Ahlskog, 1974) or dopamine mechanisms (Baez, 1974; Burridge and Blundell, 1979) seem to be implicated in the anorexic action of amphetamine, these amine systems do not appear to play a direct role in the action of fenfluramine.

Further evidence on the mode of action of fenfluramine has been produced using a continuous monitoring procedure which has revealed effects which are inaccessible in studies using deprived rats. The initial study using the Kissileff type eatometer demonstrated that amphetamine and fenfluramine gave rise to quite distinctive behavioural profiles (Blundell and Leshem, 1975), which were not readily related to the blood levels of the drugs (Blundell, Campbell, Leshem and Tozer, 1975). The characteristic effect of fenfluramine on these free-feeding rats was a reduction in meal size (Fig. 2) and the specificity of this action suggested the operation of a 5-HT-mediated satiation process (Blundell, Latham and Leshem, 1976). Subsequently, this effect of fenfluramine has been reported in a number of separate studies (Blundell and Latham, 1978; Burton, Cooper and Popplewell, 1981; Blundell and Latham, 1982; Davies, Rossi, Panksepp, Bean and Zolovick, 1983) and has been shown to occur in both obese and lean Zucker rats (Grinker, Drewnowski, Enns and Kissileff, 1980). In keeping with the initial observations (Blundell and Leshem, 1975) it has recently been affirmed that the "effects of fenfluramine are specific to the mechanisms which control meal size, with a nebligible effect upon meal initiation" (Davies *et al.*, 1983).

The power of the continuous monitoring procedure rests on its capacity to provide an accurate measure of moment to moment changes in consumption over long periods of time (usually 24 hr). In turn, these detailed profiles of consumption can be related to changes in the concentration of the drug in the blood and brain. In addition, the refinement of computer processing of feeding data (see Blundell and Latham, 1982 for details) has allowed the description of both inter- and intra-meal events (Fig. 3). In particular, fenfluramine has been shown to slow the rate of eating during the course of a meal (Blundell and Latham, 1978, 1982; Burton *et al.*, 1981). This reduction in rate of eating has also been revealed through the observational analysis of the micro-structure of eating following food deprivation (Blundell and Latham, 1978). Moreover, the slow rate of eating brought about by fenfluramine is counteracted by methergoline (Blundell and Latham, 1980). Taken together, studies on the structure of feeding behaviour following administration of fenfluramine indicate that the drug does not produce a non-specific

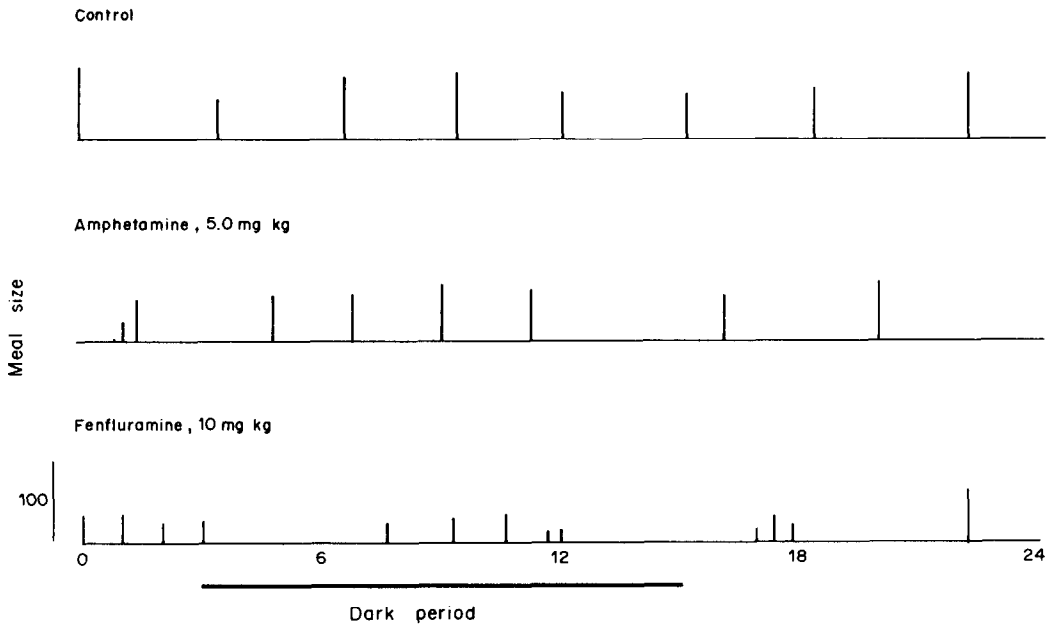


Fig. 2. Individual record of the continuous monitoring of meals over 24 hr, following injections of saline, amphetamine or fenfluramine. Each vertical line represents one meal, and the height of each line indicates the size of the meal (number of 45 mg precision food pellets). Distances between vertical lines are the inter-meal intervals.

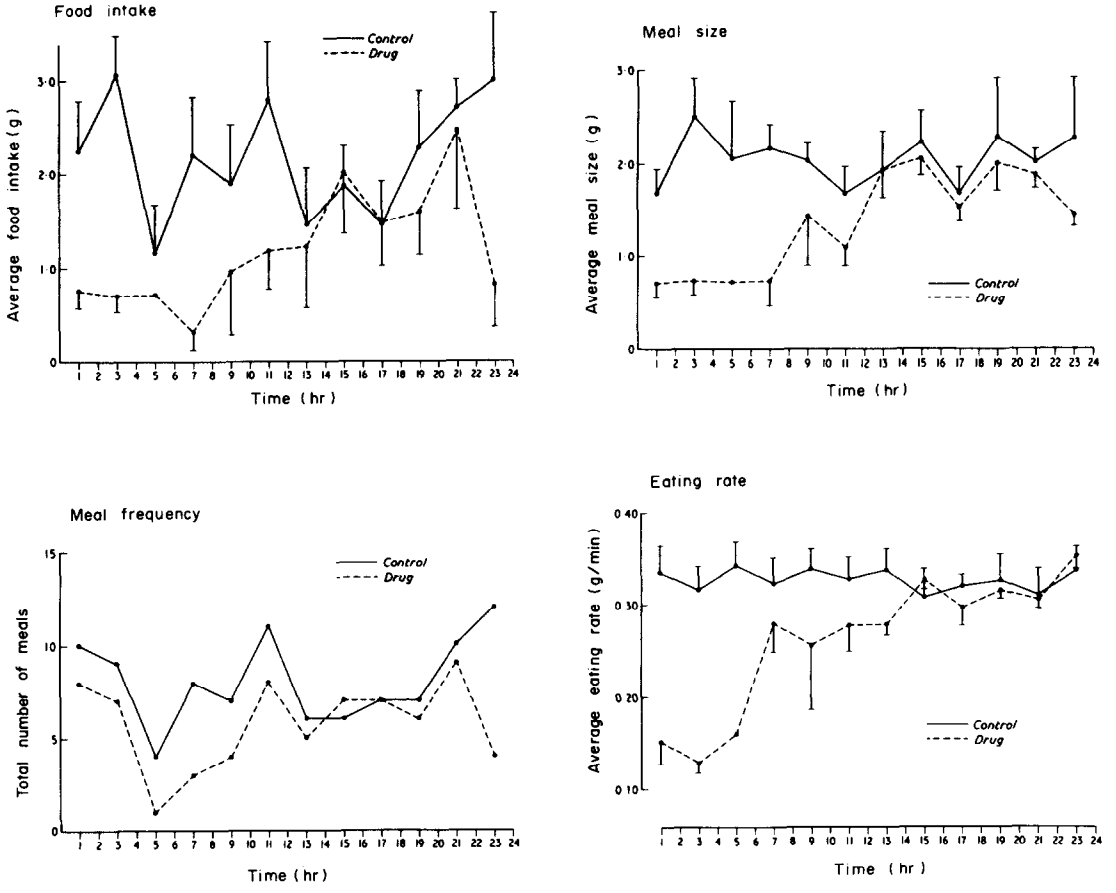


Fig. 3. Temporal profiles of feeding parameters following treatment with saline or fenfluramine (5.0 mg/kg). The data are plotted in 2-hr blocks over a 24-hr period. The time courses allow inspection of the degree of association or disengagement between different parameters.

blockade of eating nor does it introduce abnormal patterns of behaviour which could interfere with the natural expression of eating. The drug exerts an action on specific components of the feeding process and appears to produce a firm re-adjustment of the pattern of eating.

Unlike most anorexic drugs based on the phenylethylamine configuration, fenfluramine does not produce an increase in arousal but tends to display a sedative action. Since fenfluramine reduces locomotor activity in certain test situations, it has been suggested that the inhibition of eating is simply one aspect of a more general inhibitory effect of serotoninergic activation. However, elucidation of this issue requires the measurement of locomotion and feeding under similar test conditions. This can be achieved by monitoring both aspects of behaviour simultaneously. Under such circumstances in deprived animals, fenfluramine reduces food intake without producing marked changes in activity or resting (Blundell and Latham, 1980). In free-feeding rats, fenfluramine does give rise to an increase in the amount of time spent resting and asleep. However the temporal analysis of behaviour from videotaped records shows that there is no change in resting during the actual consumption of a meal nor during the appetitive phase of behaviour leading up to a meal (Blundell and McArthur, 1979). Consequently eating is not impeded by animals falling asleep or showing excessive sedation. However, once the meal has finished the post-prandial period of sleep is greatly extended. In other words the state of satiety (period of inhibition over further eating) is prolonged by fenfluramine.

Interestingly, a number of other compounds show similar actions. For example, fluoxetine, a more specific inhibitor of the 5-HT membrane pump than chlorimipramine (Fuller, Perry, Snoddy and Molloy, 1974), has been shown to potently depress food intake (Goudie, Thornton and Wheeler, 1976) and shows a behavioural profile similar to that of fenfluramine in the deprived rat (Blundell and Latham, 1978). Moreover, the blocker of uptake of 5-HT, ORG 6582 produces a dose-related reduction in meal size in the free-feeding rat (Blundell and Latham, 1978). To the extent that the suppressant action of fenfluramine on feeding is serotoninergically mediated, the experimental data suggest the existence of a 5-HT mechanism which is inhibitory and normally serves to bring feeding to a close. Taken together, the findings suggest that the facilitation of synaptic 5-HT through pharmacological manipulation represents a sufficient, though not a necessary condition for the occurrence of anorexia.

### *3.2. Receptor blockers*

A number of compounds with affinity for 5-HT receptors have been shown to block the anorexic action of a drug such as fenfluramine (e.g. Garattini and Samanin, 1976). Do such drugs influence food intake when administered alone? Methysergide, widely used in the treatment of migraine, has been reported to increase appetite with a resulting gain in weight (see Blundell, 1977). In addition, unwanted gains in weight of as much as 10 kg have been reported during treatment of migraine with the anti-serotonin compound pizotofen (BC-105; Speight and Avery, 1972). Surprisingly, increases in food intake of animals have been more difficult to detect. One possible reason for the comparative ineffectiveness of methysergide in animals is the tendency for drugs to be administered to deprived animals or animals on strict feeding regimes, which promote eating at a maximal rate. If 5-HT systems mediate in a satiation process, then the appropriate time to observe feeding effects evoked by a serotonin antagonist would be when satiation was maximal, not when satiety was weak. Significantly, methysergide has been shown to elevate food intake when given to hungry rats which have been allowed to feed freely for 30 min (Blundell and Leshem, 1974). This effect is consistent with the dissipation of satiation signals arising from food consumption.

Cyproheptadine also increases appetite and food intake in humans (Silverstone and Schuyler, 1975) and elevations of food intake and body weight have been observed in rats (Ghosh and Parvathy, 1973) and cats (Chakkrabarty, Pillai, Anand and Singh, 1976). Interestingly, when meal taking was measured in fasting rats, using a continuous recording device, cyproheptadine significantly increased the duration of the first large meal consumed after deprivation (Baxter, Miller and Soroko, 1970). This action is the converse of that brought about by fenfluramine and similar drugs, and provides further evidence that a 5-HT mechanism is somehow implicated in the control of meal size.

### *3.3. Percursors of serotonin*

Exogenously administered 5-hydroxytryptophan (5-HTP) is frequently employed as a tool to investigate serotoninergic function and there are positive and negative aspects to its use (see Blundell, 1979). In the few studies in which specific observations of food intake have been carried out, there is general agreement about the effect of 5-HTP. Joyce and Mrosovsky (1964) reported a dose-dependent reduction of food intake in satiated rats measured over a 22 hr period following interperitoneal injections of *dl*-5-HTP, and Singer, Sanghvi and Gershon (1971) showed that *l*-5-HTP (50 mg/kg) significantly depressed eating during a 1 hr food test in deprived rats. Similarly, Blundell and Leshem (1975) observed a reduction in food intake which lasted for at least 4 hr following an injection of 37.5 mg/kg *l*-5-HTP. In addition, when 5-HTP was administered together with the peripheral decarboxylase inhibitor carbidopa (MK-486), the suppressant effect on food intake remained, although there was a weak antago-

nistic effect of MK-486 (Blundell and Latham, 1979). Since changes in metabolism of 5-HTP following administration of 5-HTP and MK-486 are probably restricted to events occurring in the brain, this finding suggests that the effects of 5-HTP on feeding are mediated centrally. Interestingly, the action of 5-HTP plus MK-486 on the micro-structure of eating and on meal patterns show similar effects to those of fenfluramine and related compounds. These effects are typified by a reduction in meal size (but not meal number) and a slowing of the intra-meal eating rate (Blundell and Latham, 1979).

Because of certain methodological difficulties associated with the administration of 5-HTP, the technique of tryptophan loading is often preferred as a means of elevating levels of 5-HT brain. One early report of a dose-dependent decrease in food consumption after peripheral injections of tryptophan (see Fernstrom and Wurtman, 1972, note 14), has been followed by further confirmation of this effect (Latham and Blundell, 1979; Gibbons, Barr, Bridger and Leibowitz, 1981) though negative reports have also been published (Weinberger, Knapp and Mandell, 1978; Peters, Bellissimo and Harper, 1984). What factors could account for this disagreement concerning the effect of tryptophan? One possibility concerns the sensitivity of the behavioural assay used to measure feeding. The effect of tryptophan on food intake is not massive (at the moderate dose normally administered) and any disturbance or contamination during collection of data could easily mask the anorexic action. Significantly, when the effects of tryptophan were monitored continuously in a controlled laboratory environment, a clear effect was demonstrated on free-feeding rats which lasted for 4 hr after administration. This effect was characterised by a reduction in meal size. Moreover, in deprived rats, tryptophan reduced the magnitude of the first enormous meal normally consumed by rats when allowed access to food (Latham and Blundell, 1979). Interestingly, the post-meal interval was significantly extended, indicating that tryptophan not only reduced meal size but also intensified inhibition over further eating. Taken together, the actions of precursors of serotonin are generally consistent with the effects of other pharmacological manipulations which facilitate 5-HT synaptic transmission.

#### 4. LESIONS AND DEPLETIONS OF BRAIN SEROTONIN SYSTEMS

Effects of central manipulations on the anorexia induced by peripherally-administered drugs have been described earlier. However, it is important to consider whether such manipulations, which adjust 5-HT in brain have any direct effect on food intake or feeding parameters.

When injected systemically, *p*-chlorophenylalanine (*p*CPA) produces a variety of changes in food consumption, some of which may be dependent upon various intestinal disturbances (see Blundell, 1979). However, when *p*CPA was injected bilaterally into the cerebral ventricles of rats it produced a marked depletion of serotonin in brain with only small decrements in noradrenaline and dopamine; more importantly the treatment gave rise to a clear hyperphagia with a concomitant increase in body weight (Breisch and Hoebel, 1975; Breisch, Zemlan and Hoebel, 1976). However, since a similar effect was later observed with other methyl esters (Coscina, Daniel and Warsh, 1978; Mackenzie, Hoebel, Ducret and Trulson, 1979), it appears that the weight gain is not dependent upon a decrease in serotonin in whole brain. Using neurotoxins, it has been shown that intraventricular injections of 5,6-dihydroxytryptamine produced a dose-dependentincrease in food consumption (Diaz, Ellison and Masouka, 1974), whilst 5,7-dihydroxytryptamine (5,7-DHT) gave rise to a long-lasting hyperphagia and weight gain (Saller and Stricker, 1976). This last effect was also associated with increased growth, consequently the effect may be only obliquely related to the regulation of food intake.

In addition to the use of neurotoxins, extensive correlational analyses have been performed between neurochemical changes and adjustments in food intake following micro-knife cuts in the midbrain tegmentum (Grossman, Grossman and Halaris, 1977) and in various segments of the media forebrain bundle (McDermott, Alheid, Halaris and Grossman, 1977). In the first study, all of the cuts significantly depleted noradrenaline and 5-HT in the hypothalamus and forebrain. However, the only significant correlation revealed that hyperphagia was associated with a depletion of 5-HT in the forebrain. The second study revealed that ingestive behaviour (including both aphagia and hyperphagia) was positively correlated with 5-HT in the forebrain. Accordingly, these studies provide some of the best evidence for a relationship between serotonin in brain and food intake but also suggest an interaction between 5-HT in forebrain and dopaminergic pathways in the overall regulation of food intake.

In view of these data, it is rather surprising that only slight changes in feeding have been noticed following lesions of the raphe nuclei, which markedly deplete 5-HT in forebrain (see Blundell, 1979 for discussion). It does appear likely that the precise location of the lesion within the raphe system is a critical factor. In keeping with this consideration, it is important to note that specific lesions of the B8 raphe nuclei have been shown to increase body weight whereas B7 and B9 lesions have no effect (Geyer, Puerto, Dawsey, Knapp and Bullard, 1976). Rats operated at 6 weeks of age, and sacrificed 4 weeks later, showed mean weight gains for controls, B7, B8 and B9 of 95.0, 94.9, 120.0 and 96.0 g.

The importance of the site of depletion is also emphasized by the results of local injections of 5,7-DHT. Bilateral micro-infusions of 5,7-DHT into

the ventro-lateral hypothalamus brought about substantial depletion of serotonin in the septum, hippocampus and hypothalamus. Those rats which became hyperphagic displayed both hippocampal and hypothalamic depletion (Waldbilling, Bartness and Stanley, 1981). Since the knife-cut experiments mentioned above failed to show a correlation between 5-HT in the hypothalamus and ingestive behaviour, these studies taken together suggest that the hippocampus may be an important zone for the actions of 5-HT. However, there is one further interesting feature of the Waldbilling *et al.* (1981) experiment. The stable hyperphagia did not occur whilst rats consumed their normal laboratory chow but only appeared when a high fat diet was introduced. Such high fat diets are not only calorically dense but are also highly palatable; they differ from chow on the basis of nutrient composition, energy density, sensory qualities (taste and texture) and acceptibility. Such diets are often used to induce experimental obesity. According to the results of this study it appears that depletion of serotonin augments the capacity of a highly perferred diet to increase consumption and to facilitate weight gain. As noted earlier (see Section 2) this experiment shows the importance of using a number of behavioural procedures for the investigation of neurochemistry and food intake.

This interaction between central manipulation of serotonin and composition of diet may account for a number of the negative findings following depletion of serotonin in brain. It should be considered that in most experiments laboratory rats are maintained on a composite chow diet, often in powdered form. Such a low palatability diet may work against treatments which enhance consumption, but favour manipulations which suppress intake. In addition, differences between the effects created by administration of neurotoxin (local of diffuse), knife cut and raphe lesions could be accounted for by differences in the overall depletion of 5-HT, the extent of receptor supersensitivity which may occur following axon degeneration (Trulson, Eubanks and Jacobs, 1976), the extent of regrowth of damaged axons (Nobin and Bjorklund, 1978), regional differences in 5-HT loss and supersensitivity, and the selective destruction and survival of particular sub-types of 5-HT receptors. At the present time, certain results of central manipulations of 5-HT strongly support the involvement of 5-HT in brain in the control of food intake, whilst others offer no confirmation. This discord may be resolved when some of the methodological variables mentioned above are systematically examined.

### 5. CENTRAL MICRO-INJECTIONS

Local injections of neurotoxins, mentioned above, have demonstrated the usefulness of the procedure for selectively manipulating brain chemistry. More commonly, the technique has been employed to examine the direct action upon the brain of these agents described in 3.1 and 3.2 which produce significant effects on feeding when injected peripherally. A number of experiments have injected large doses of 5-HT into the ventricles or directly into specific loci. These studies have been previously reviewed (Blundell, 1977, 1979) and often can be criticised for injecting amounts of 5-HT many times more than the total content of the transmitter in the brain. More recently, much smaller doses have been used and their administration has been guided by research emphasising the importance of the paraventricular nucleus (PVN) in the medial hypothalamus and the perifornical (PF) zone, situated more laterally. It is here that injections of catecholamines produce the most intense effects on food intake (Leibowitz, 1980; Hoebel and Leibowitz, 1981). Most importantly, feeding may be reliably induced by injections of noradrenaline (NA) into the paraventricular nucleus and blocked by the administration of dopamine or adrenaline into the perifornical zone.

The injection of 5-HT into the paraventricular nucleus inhibited feeding without effects on general arousal (Leibowitz and Papadakos, 1978). In food-deprived rats, doses between 1 and 10 $\mu$g produced a reliable dose-dependent suppression of up to 50% during a 60 min period after injection. A more potent inhibitory effect was displayed in satiated rats which had been induced to eat by injections of NA into the paraventricular nucleus. When 5-HT was injected into the paraventricular nucleus immediately prior to NA, the eating response to NA was reduced by 90%. This effect occurred reliably with a dose of 5-HT as small as 100 ng. Tests with receptor antagonists injected into the paraventricular nucleus immediately prior to 5-HT, disclosed a dose-dependent antagonism of the action of 5-HT by methysergide and cinanserin. However, the effect could also be countered by administration of certain $\beta$-adrenergic blockers and phenothiazine-type dopamine antagonists. These effects may indicate a strong affinity of $\beta$-adrenergic and dopaminergic antagonists for 5-HT receptors and may provide a route for the investigation of the particular sub-type of 5-HT receptor involved in anorexia at this site. Leibowitz (1980) argues in favour of a specific 5-HT receptor-mediated response, and a model as been put forward (Fig. 4) to describe the control of feeding by an interaction between transmitters in the paraventricular nucleus and perifornical zone (Hoebel and Leibowitz, 1981).

In addition to the direct injection of 5-HT, 5-HTP injected into the paraventricular nucleus has also been shown to antagonise eating induced by NA (Leibowitz and Papadakos, 1978). The effect was dose dependent, occurring reliably at a dose as small as 100 ng, and the suppression of intake was countered by prior central injections of the decarboxylase inhibitors benserazide (RO 4-4602) and MK-486. Moreover, all of the agents mentioned in Section 3.1 which inhibit feeding when injected peripherally (fenfluramine, norfenfluramine, fluoxetine and quip-

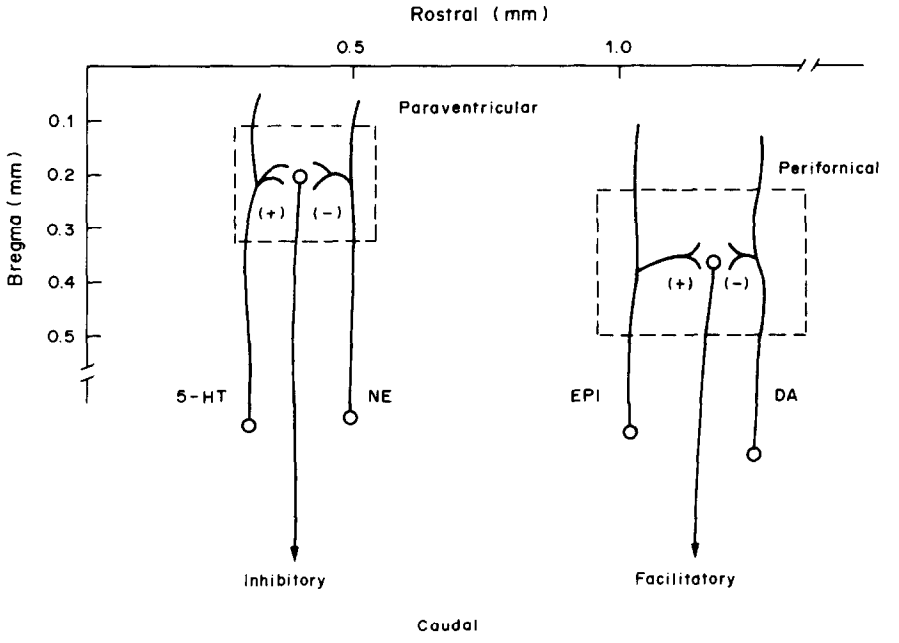


Fig. 4. Summary of evidence on hypothalamic neurotransmitters involved in the facilitation and inhibition of food intake (after Hoebel and Leibowitz, 1981).

azine) also suppress NA-induced and deprivation-induced feeding when injected into the paraventricular nucleus. Taken together these data point to the existence of endogenous stores of 5-HT within the paraventricular nucleus which are important in the inhibition of eating.

### 6. 5-HT AND NUTRIENT SELECTION

In addition to a postulated action on total food intake and the structure of feeding behaviour, it has also been suggested that 5-HT plays a role in the selection of macronutrients, particularly protein and carbohydrate. The underlying principle is based on the relationship between dietary composition, plasma ratios of amino acids (particularly the ratio of tryptophan to large neutral amino acids), uptake of tryptophan into the brain and enhancement of the synthesis of serotonin. The evidence for this view has been set out elsewhere (e.g. Anderson, 1979; Wurtman, Heftl and Melamed, 1981) and the operation of the mechanism implies that the concentration of 5-HT in brain depends upon the nutrient composition of the diet consumed. Tryptophan is alleged to play a crucial role in this mechanism and a number of objections have been raised against the process (Peters *et al.*, 1984; Curzon, 1984). However, the hypothesis suggests that manipulations of metabolism of serotonin or of concentrations of 5-HT in brain should bring about an adjustment of the animal's capacity to voluntarily self-select particular nutrients. Obviously, an experimental test of this possibility requires a test situation allowing animals the opportunity to make dietary choices (see Section 2.2).

The first experiments using peripherally-administered agents were directly related to the proposed role for serotonin in protein selection (Wurtman and Wurtman, 1977). The purpose of the experiments was to separate the effects of drugs on total caloric intake from their effects on the consumption of a particular nutrient. In the major study male weanling rats (21–48 days old) were placed on an 8-hr cyclic feeding regimen and during the feeding period allowed to select food from two isocaloric diets, containing 5 or 45% protein. The rats were injected with one of two drugs, fenfluramine and fluoxetine, known to act on serotonin metabolism. With fenfluramine no adjustments were observed during the first hour after injection, but during the following 3 hr "fenfluramine-treated animals selectively decreased their consumption of the low-protein diet and increased their consumption of the high-protein food so that total caloric intake was depressed while protein intake was spared". Like fenfluramine, fluoxetine suppressed food intake but spared protein consumption, thereby increasing the proportion of calories consumed as protein. On the other hand amphetamine, a drug with little known action on serotonin-mediated neurotransmission, was reported to reduce food consumption but failed to alter the proportion of total calories consumed as protein. The action of serotoninergic drugs was characterised as a protein sparing effect (Wurtman and Wurtman, 1977).

These first studies were carried out on young rats subjected to food deprivation prior to testing. To investigate the robustness of the findings, Blundell and McArthur (1979) administered fenfluramine to

adult rats maintained on a deprivation regimen or allowed to feed freely. For deprived animals the data were broadly in keeping with the findings of Wurtman and Wurtman (1977); fenfluramine gave rise to an increase in the proportion of protein in the total food consumed (protein-sparing effect). However, under free feeding conditions, the protein-sparing effect of fenfluramine was not apparent. It has since been revealed that food deprivation significantly decreases intake of protein and the ratio of protein to total energy consumed in both adult and weanling rats (McArthur and Blundell, 1982). The alteration of this baseline should be considered in evaluating the effects of drugs on nutrient intake. In addition, it has also been demonstrated that sensory characteristics of the diet can exert a significant effect on the action of drugs to alter protein intake (Blundell, 1983). This factor may have had some bearing on the outcome of a further experiment in which fenfluramine was adminstered to rats, offered a choice of pure separate portions of protein (casein), carbohydrate (corn starch and dextrin) and fat (vegetable fat and safflower oil). In one experiment in which the fat ration contained more calories than the other two nutrient ratios, fenfluramine reduced the intake of protein and fat and tended to spare carbohydrate. When all diets were made isocaloric, fat intake was again severely depressed with a relative and weak sparing of protein and carbohydrate (Orthen-Gambill and Kanarek, 1982). If animals are given diets containing different proportions of two nutrients and if the treatment selectively alters their intake of one of the diets, it may not be clear which of the nutrients the animal is choosing or avoiding. For example, if a treatment causes rats to consume less of a diet A (high-carbohydrate, low-protein) than diet B (low-carbohydrate, high protein), it can be said to be exerting either a "protein-sparing" or a "carbohydrate-suppressing" effect. A decision about which action is primary and which secondary requires the use of different types of test diets in which only one of the nutrients in question is varied. In experiments (Wurtman and Wurtman, 1979) on the effect of serotoninergic drugs on carbohydrate intake, rats were allowed to consume from two isocaloric, iso-protein diets containing either 25 or 75% dextrin. Following administration of fenfluramine or MK212, rats specifically decreased their consumption of the high (75%)-carbohydrate diet and consumed relatively more of the low-carbohydrate diet. Consequently, the absolute intake of carbohydrate was reduced, together with the proportion of total food represented by carbohydrate. The role of serotonin may be to control the proportion of carbohydrate to protein consumed rather than absolute amounts. It should be noted that the depression of fat intake by fenfluramine was not observed in these experiments; with these iso-protein diets the preferred low carbohydrate diet actually contained a high proportion of fat.

In a specific test of the effect of tryptophan on nutrient selection, the amino acid (100 mg/kg) was administered to rats allowed to choose between 0 and 55% or 15 and 55% protein diets (Peters *et al.*, 1984). Although the concentrations of 5-HT and 5-HTAA in brain increased by 50%, the treatment with tryptophan did not modify total food intake or protein and carbohydrate selection. However, other manipulations of 5-HT in brain synthesis blockers, neurotoxins and raphe lesions have produced quite different results. Following systemic administration of *p*CPA, intraventricular injections of 5-7,DHT or radio-frequency lesions of dorsal and medial raphe nuclei, whole brain content of 5-HT was reduced and the rats consumed a smaller proportion of protein in their total intake (Ashley, Coscina and Anderson, 1979). These data support a role for 5-HT in nutrient selection, but one puzzle is that these changes in protein intake are in the opposite direction to that predicted by some previous *post hoc* correlations of dietary selection and plasma tryptophan to neutral amino acid ratios (Ashley and Anderson, 1975a,b).

Clearly, the overall picture is somewhat complex and the investigation of nutrient selection is beset by severe methodological difficulties (Blundell, 1983). Different studies, involving differences in the age of animals, sensory qualities of diets, concentration of nutrients, type of nutrient offered, number of choices, feeding regimens and test intervals, have produced widely varying results. The protein sparing (or carbohydrate suppressive) action of fenfluramine and similar drugs can be observed under certain conditions but does not appear to be a very robust phenomenon. Taken together the evidence suggests that fluctuations in 5-HT in brain (probably in certain selective sites) create a disposition to modulate dietary selection, but that this tendency may be blocked or masked by changes in physiological or environmental circumstances (see Blundell, 1983 for further discussions of these issues and review of human experiments).

### 7. A NOTE ON CENTRAL VERSUS PERIPHERAL EFFECTS

Although manipulations of 5-HT in brain produce clear effects on feeding behaviour, the presence of different types of 5-HT receptors at critical sites in the gastro-intestinal region invites the supposition that at least a part of the adjustment in consumption (or selection) could be provoked by peripheral action. For fenfluramine, it has been argued that the anorexic action, at least in non-deprived animals, may be related to a slowing of gastric emptying (Davies, 1976; Davies *et al.*, 1983). Fenfluramine does slow stomach emptying and was shown to be most effective in lengthening the post-meal interval when given immediately after feeding. In addition, it has been known for more than ten years that peripheral injections of 5-HT inhibit food intake. Bray and

York (1972) reported that 5-HT (12.5 mg/100 g body weight) reduced food consumption in normal rats, Zucker fat rats, and rats made hyperphagic by lesions of the ventromedial hypothalamus. More recently the anorexia following intraperitoneal injections of 5-HT has been shown to be dose-dependent (Pollock and Rowland, 1981) and is blocked by methysergide but not by methergoline (Fletcher and Burton, 1984). Moreover, the anorexia is not countered by a sub-diaphragmatic vagotomy (Simansky, Bourbonais and Smith, 1982). At the moment the contribution made to the control of food intake by alterations in peripheral 5-HT have been only sparingly investigated.

## 8. CONCLUSIONS

Results of experiments on animals, together with human clinical evidence (not discussed here), clearly show that manipulations of 5-HT metabolism can, under certain conditions, produce marked changes in food intake, food preferences and body weight. These data must be interpreted cautiously for they do not *prove* that 5-HT systems contribute to the natural processes controlling feeding behaviour. However, on the basis of these findings various researchers have suggested that serotonin: (a) plays an inhibitory role in feeding and is selectively involved in satiation (Blundell, 1977); (b) contributes to the day and night control of satiety (Hoebel, 1977); (c) may modulate other systems regulating body weight (Coscina, 1977); (d) interacts reciprocally with dopamine in the control of ingestive behaviour (McDermott *et al.*, 1977); (e) regulates the intake of protein (Anderson, 1979); (f) controls the relative proportions of protein and carbohydrate (Fernstrom and Wurtman, 1973). In addition, it has been postulated that serotonin systems play some part in the syndrome of effects following medial hypothalamic damage and contribute to the pattern of behaviour after lateral hypothalamic lesions. It is absolutely clear that feeding activities are not solely under the control of 5-HT mechanisms. The specific adjustments to feeding brought about by manipulations of 5-HT combine with the actions of other neurotransmitters to produce the ultimately observed pattern of feeding behaviour. The neurotransmitter interactions underlying feeding are complex (see Blundell, 1982, for reveiw). It is within this framework that the function of particular sub-types of 5-HT receptors in the expression of eating should be sought.

## REFERENCES


Ahlman H. (1976) Fluorescence histochemical studies on serotonin in the small intestine and the influence of vagal nerve stimulation. *Acta physiol. scand.* 437.

Ahlskog J. E. (1974) Food intake and amphetamine anorexia after selective forebrain norepinephrine loss. *Brain Res.* **82:** 211–240.

Ahlskog J. E., Randall P. K., Hernandez L. and Hoebel B. G. (1984) Loss of amphetamine anorexia after midbrain 6-hydroxydopamine with opposite effect on fenfluramine anorexia. *Psychopharmacology* In press.

Anderson G. H. (1979) Control of protein and energy intake: role of plasma amino acids and brain neurotransmitters. *Can. J. Physiol. Pharmac.* **57:** 1043–1057.

Ashley D. V. M. and Anderson G. H. (1975a) Food intake regulation in the weanling rat: effects of the most limiting essential amino acids of gluten, casein and zein on the self-selection of protein and energy. *J. Nutr.* **105:** 1405–1411.

Ashley D. V. M. and Anderson G. H. (1975b) Correlation between the plasma tryptophan to neutral amino acid ratio and protein intake in the self-selecting weanling rat. *J. Nutr.* **105:** 1412–1421.

Ashley D. V. M., Coscina D. V. and Anderson G. H. (1979) Selective decrease in protein intake following brain serotonin depletion. *Life Sci.* **24:** 973–984.

Azmitia E. C. (1978) The serotonin-producing neurons of the midbrain median and dorsal raphe nuclei. In: *Handbook of Psychopharmacology* Vol. 9 (Iversen L. L., Iversen S. D. and Snyden S. H., Eds), pp. 233–314. Plenum Press, New York.

Baez L. A. (1974) Role of catecholamines in the anorexic effects of amphetamine in rats. *Psychopharmacology* **35:** 91–96.

Barchas J. and Usdin E. (Eds) (1973) *Serotonin and Behaviour.* Academic Press, New York.

Barrett A. M. and McSharry L. (1973) Inhibition of drug-induced anorexia in rats by methysergide. *J. Pharm. Pharmac.* **27:** 889–895.

Baxter M. G., Miller A. A. and Soroko F. E. (1970) The effect of cyproheptadine on food consumption in the fasted rat. *Br. J. Pharmac.* **39:** 229–230.

Benady D. R. (1970) Cyproheptadine hydrochloride (Periactin) and anorexia nervosa: a case report. *Br. J. Psychiat.* **117:** 681–682.

Blundell J. E., Latham C. J. and Leshem M. B. (1973) Biphasic action of a 5-hydroxytryptamine inhibitor on fenfluramine induced anorexia. *J. Pharm. Pharmac.* **25:** 492–494.

Blundell J. E. and Leshem M. B. (1973) Dissociation of the anorexic effects of amphetamine and fenfluramine following intrahypothalamic injection. *Br. J. Pharmac.* **47:** 183–185.

Blundell J. E. and Leshem M. B. (1974) Central action of anorexic agents: effects of amphetamine and fenfluramine in rats with lateral hypothalamic lesions. *Eur. J. Pharmac.* **28:** 81–88.

Blundell J. E., Campbell D. B., Leshem M. B. and Tozer R. (1975) Comparison of the time course of the anorexic effects of amphetamine and fenfluramine with drug levels in blood. *J. Pharm. Pharmac.* **27:** 197–192.

Blundell J. E. and Leshem M. B. (1975a) Analysis of the mode of action of anorexic drugs. In: *Recent Advances in Obesity Research I* (Howard A., Ed.), pp. 368–371. Newman, London.

Blundell J. E. and Leshem M. B. (1975b) The effect of 5-hydroxytryptophan on food intake and on the anorexic action of amphetamine and fenfluramine. *J. Pharm. Pharmac.* **27:** 31–37.

Blundell J. E., Latham C. J. and Leshem M. B. (1976) Differences between the anorexic actions of amphetamine and fenfluramine—possible effects on hunger and satiety. *J. Pharm. Pharmac.* **28,** 471–477.

Blundell J. E. (1977) Is there a role for serotonin (5-hydroxytryptamine) in feeding? *Int. J. Obes.* **1:** 15–42.

Blundell J. E. and Latham C. J. (1978) Pharmacological manipulation of feeding behaviour: possible influences of serotonin and dopamine on food intake. In: *Central Mechanisms of Anorectic Drugs* (Garattini S. and Samanin R., Eds), pp. 83–109. Raven Press, New York.

Blundell J. E. (1979a) Hunger, appetite and satiety—constructs in search of identities. In: *Nutrition and Life-*

*styles* (Turner M., Ed.), pp. 21–42. Applied Science, London.

Blundell J. E. (1979b) Serotonin and feeding. In: *Serotonin in Health and Disease*, Vol. 5 *Clinical Applications* (Essman W. B., Ed.), pp. 403–450. Spectrum, New York.

Blundell J. E. and Latham C. J. (1979a) Pharmacology of food and water intake. In: *Chemical influences on Behaviour* (Cooper S. and Brown K., Eds), pp. 201–254. Academic Press, London.

Blundell J. E. and Latham C. J. (1979b) Scrotonergic influences on food intake: effect of 5-hydroxytryptophan on parameters of feeding behaviour in deprived and free-feeding rats. *Pharmac. Biochem.* **11:** 431–437.

Blundell J. E., Latham C. J., McArthur R. A., Moniz E. and Rogers P. J. (1979) Structural analysis of the action of amphetamine and fenfluramine on food intake and feeding behaviour in animals and man. *Curr. med. Res. Opin.* **6:** 34–54.

Blundell J. E. and McArthur R. A. (1979) Investigation of food consumption using a dietary self-selection procedure: effects of pharmacological manipulation and feeding schedules. *Br. J. Pharmac.* **67:** 436P–438P.

Blundell J. E. (1980) Pharmacological adjustment of the mechanisms underlying feeding and obesity. In: *Obesity* (Stunkard A. J., Ed.), pp. 182–207. Saunders, Philadelphia.

Blundell J. E. and Latham C. J. (1980) Characterisation of the adjustments to the structure of feeding behaviour following pharmacological treatment: effects of amphetamine and fenfluramine and the antagonism produced by pimozide and methergoline. *Pharmac. Biochem. Behav.* **12:** 717–722.

Blundell J. E. (1981a) Deep and surface structures: a qualitative approach to feeding. In: *The Body Weight Regulatory System: Normal and Disturbed Mechanisms* (Cioffi L. A., James W. P. T. and Van-Itallie T., Eds), pp. 73–82. Raven Press, New York.

Blundell J. E. (1981b) Biogrammar of feeding: pharmacological manipulations and their interpretations. In: *Progress in Theory in Psychopharmacology* (Cooper S. J., Ed.), pp. 233–276. Academic Press, London.

Blundell J. E. and McArthur R. A. (1981) Behavioral flux and feeding: continuous monitoring of food intake and food selection and the video-recording of appetitive and satiety sequences for the analysis of drug action. In: *Anorectic Agents, Mechanisms of Action and of Tolerance* (Garattini S., Ed.), pp. 19–34. Raven Press, New York.

Blundell J. E. (1982) Neuroregulators and feeding: implications for the pharmacological manipulation of hunger and appetite. *Rev. Pure appl. Pharmac. Sci.* **3:** 381–462.

Blundell J. E. and Latham C. J. (1982) Behavioural pharmacology of feeding. In: *Drugs and Appetite* (Silverstone T., Ed.), pp. 41–80. Academic Press, London.

Blundell J. E. (1983) Processes and problems underlying the control of food selection and nutrient intake. In *Nutrition and the Brain*, Vol. 6 (Wurtman R. J. and Wurtman J. J., Eds), pp. 163–221. Raven Press, New York.

Booth D. A. (1976) Localization of the adrenergic feeding system in the rat diencephalon. *Science* **158:** 515–517.

Bray G. A. and York D. A. (1972) Studies on food intake in genetically obese rats. *Am. J. Physiol.* **233:** 176–179.

Breisch S. T. and Hoebel B. G. (1975) Hyperphagia and transient obesity following intraventricular parachlorphenylalanine. *Fedn Proc. Fedn Am. Socs exp. Biol.* **34:** 296.

Breisch S. T., Zemlan F. P. and Hoebel B. G. (1976) Hyperphagia and obesity following serotonin depletion by intraventricular parachlorophenylalanine. *Science* **192:** 382–384.

Burridge S. L. and Blundell J. E. (1979) Amphetamine anorexia: antagonism by typical but not atypical neuroleptics. *Neuropharmacology* **18:** 453–457.

Burton M. J., Cooper S. J. and Popplewell D. A. (1981) The effect of fenfluramine on the microstructure of feeding and drinking in the rat. *Br. J. Pharmac.* **69:** 621–633.

Carey R. J. and Goodall E. B. (1975) Attentuation of amphetamine anorexia by unilateral nigro-striatal lesions. *Neuropharmacology* **14:** 827–834.

Carey R. J. (1976) Effects of selective forebrain depletions of norepinephrine and serotonin on the activity and food intake effects of amphetamine and fenfluramine. *Pharmac. Biochem. Behav.* **5:** 519–523.

Chakkrabarty A. S., Pillai R. V., Anand B. K. and Singh B. (1976) Effect of cyproheptadine on the electrical activity of the hypothalamic feeding centres. *Brain Res.* **6:** 561–569.

Clineschmidt B. V. (1973) 5,6-Dihydroxytryptamine: suppression of anorexigenic effect of fenfluramine. *Eur. J. Pharmac.* **24:** 405–409.

Clineschmidt B. V., McGuffin J. C. and Werner A. B. (1974) Role of monoamines in the anorexigenic actions of fenfluramine, amphetamine and *p*-chloromethamphetamine. *Eur. J. Pharmac.* **27:** 313–323.

Cooper P. J. and Fairburn C. G. (1983) Binge-eating and self-induced vomiting in the community: a preliminary study. *Br. J. Psychiat.* **142:** 139–144.

Cooper S. J. (1980) Benzodiazepines as appetite-enhancing compounds. *Appetite* **1:** 7–19.

Coscina D. V. (1977) Brain amines in hypothalamic obesity. In: *Anorexia Nervosa* (Vigersky R. A., Ed.), pp. 97–107. Raven Press, New York.

Coscina D. V., Daniel J. and Warsh J. J. (1978) Potential non-serotonergic basis of hyperphagia elicited by intraventricular *p*-chlorophenylalanine. *Pharmac. Biochem. Behav.* **9:** 791–797.

Coscina D. V., McArthur R. A., Stancer H. C. and Godse D. D. (1978) Association of altered brain norepinephrine and serotonin with the obesity induced by gold-thioglucose in mice. *Pharmac. Biochem. Behav.* **9:** 123–128.

Curzon G., Joseph M. H. and Knott P. J. (1972) Effects of immobilization and food deprivation on rat brain tryptophan metabolism. *J. Neurochem.* **19:** 1967–1974.

Curzon G. (1984) Effect of food intake on brain transmitter amines. In: *Psychopharmacology of Food* (Sandler M. and Silverstone T., Ed.). Oxford University Press, London. In press.

Davies R. F.(1976) Some neurochemical and physiological factors controlling free feeding patterns in the rat. Ph.D. thesis. McGill University, Montreal.

Davies R. F., Rossi J., Panksepp J., Bean N. J. and Zolovick A. J. (1983) Fenfluramine anorexia: a peripheral locus of action. *Physiol. Behav.* **30:** 723–730.

Diaz J., Ellison G. and Masuoka D. (1974) Opposed behaviour syndromes in rats with partial and more complete central serotonergic lesions made with 5,6-dihydroxytryptamine. *Psychopharmacologia* **37:** 67–69.

Dillettuso B. A. and Wangsness P. J. (1977) Effect of age on hyperphagia in the genetically obese Zucker rat. *Proc. Soc. exp. Biol. Med.* **154:** 1–5.

Edwards J. G. (1977) Unwanted effects of psychotropic drugs. IV Drugs for anxiety. *Practitioner* **219:** 117–121.

Fernstrom J. D. and Wurtman R. J. (1972) Brain serotonin content: physiological regulation by plasma neutral amino acids. *Science* **178:** 414–416.

Fernstrom J. D. and Wurtman R. J. (1973) Control of brain 5-HT content by dietary carbohydrates. In: *Serotonin and Behaviour* (Barchas J. and Usdin E., Eds), pp. 121–128. Academic Press, New York.

Fibiger H. C., Zis A. P. and McGeer E. G. (1973) Feeding and Drinking deficits after 6-hydroxydopamine administration in the rat: similarities to the lateral hypothalamic syndrome. *Brain* **55:** 135–148.

Finkelstein J. A., Chance W. T. and Fischer J. E. (1983) Brain serotonergic activity and plasma amino acid levels

in the genetically obese Zucker rats. *Pharmac. Biochem. Behav.* **17:** 939–944.

Fletcher P. J. and Burton M. J. (1984) Effects of manipulations of peripheral serotonin on feeding and drinking in the rat. *Pharmac. Biochem. Behav.* In press.

Fozard J. R. (1984) Neuronal 5-HT receptors in the periphery. *Neuropharmacology* **23:** 1473–1486.

Fuller R. W., Perry K. W., Snoddy H. D. and Molloy B. B. (1974) Comparison of the specificity of 3-(*p*-trifluoromethylphenoxy)-*N*-methyl-3-phenylpropano lamine and chlorimipramine as amine uptake inhibitors in mice. *Eur. J. Pharmac.* **28:** 223–236.

Funderburk W. H., Hazelwood J. C., Ruckhart R. T. and Ward J. W. (1971) Is 5-hydroxytryptamine involved in the mechanism of action of fenfluramine? *J. Pharm. Pharmac.* **23:** 468–469.

Fuxe K., Farnebo C. O., Hamberger B. and Ogren S. O. (1975) On the *'in vivo'* and *'in vitro'* actions of fenfluramine and its derivatives on central monoamine neurons, especially 5-hydroxytryptamine neurons, and their relation to the anorectic action of fenfluramine. *Postgrad. med. J.* **51:** 35–45.

Gal E. M., Morgan M. and Marshall F. D. (1965) Studies on the metabolism of 5-hydroxytryptamine (serotonin) III. The effect of goldthioglucose (GTG) induced obesity. *Life Sci.* **3:** 373–378.

Garattini S. and Samanin R. (1976) Anorectic drugs and neuro-transmitters. In: *Food Intake and Appetite* (Silverstone T., Ed.), pp. 82–108. Dahlem Konferenzen, Berlin.

Garattini S. (1978) Importance of serotonin for explaining the action of some anorectic agents. In: *Recent Advances in Obesity Research:* Vol. II (Bray G. A., Ed.), pp. 433–441. Newman, London.

Garrow J. (1982) Does plumpness matter? *Nutr. Bull.* **7:** 49–53.

Garthwaite T. L., Kahlkoff R. K., Gaunsing A. R., Hagan T. C. and Menahan L. A. (1979) Plasma free tryptophan, brain serotonin and an endocrine profile of the genetically obese hyperglycaemic mouse of 4–5 months of age. *Endocrinology* **105:** 1178–1182.

Gershon M. D. and Dreyfus C. F. (1977) Serotonergic neurons in the mammalian gut. In: *Nerves and the Gut* (Brooks F. P. and Evers P. W., Eds), pp. 197–206.

Geyer M. A., Puerto A., Dawsey W. J., Knapp and Bullard S. (1976) Histological and enzymatic studies of the mesolimbic and mesostriatal serotonergic pathways. *Brain Res.* **106:** 241–256.

Ghosh M. N. and Parvathy S. (1973) The effect of cyproheptadine on water and food intake and on body weight in the fasted adult and weanling rats. *Br. J. Pharmac.* **48:** 328–329.

Gibbons J. L., Barr G. A., Bridger W. H. and Leibowitz S. F. (1981) L-Tryptophan's effects on mouse killing, feeding, drinking, locomotion and brain serotonin. *Pharmac. Biochem. Behav.* **15:** 201–206.

Goudie A. J., Thornton E. W. and Wheeler T. J. (1976) Effects of Lilly 110140, a specific inhibitor of serotonin uptake, on food intake and on 5-hydroxytryptophan induced anorexia. Evidence for serotonergic inhibition of feeding. *J. Pharm. Pharmac.* **28:** 318–320.

Grinker J. A., Drewnowski A., Enns M. and Kissileff H. (1980) Effects of *d*-amphetamine and fenfluramine on feeding patterns and activity of obese and lean Zucker rats. *Pharmac. Biochem. Behav.* **12:** 265–275.

Grossman S. P. (1962) Direct adrenergic and cholinergic stimulation of hypothalamic mechanisms. *Am. J. Physiol.* **202:** 872–882.

Grossman S. P., Grossman L. and Halaris A. (1977) Effects on hypothalamic and telencephalic NE and 5-HT of tegmental knife cuts that produce hyperphagia and hyperdipsia in the rat. *Pharmac. Biochem. Behav.* **6:** 101–106.

Hoebel B. G. (1977) Pharmacologic control of feeding. *A. Rev. Pharmac. Toxic.* **17:** 605–621.

Hoebel B. G. and Leibowitz S. F. (1981) Brain monoamines in the modulation of self-stimulation, feeding and body weight. In: *Brain, Behavior and Bodily Disease* (Weiner H. A., Hoffer M. A. and Stunkard A. J., Eds), pp. 103–142. Raven Press, New York.

Hoebel R. G., Zemlan F. P., Trulson M. E., McKenzie R. G., Ducret R. P. and Norelli C. (1978) Differential effects of *p*-chlorophenylalanine and 5,7-dihydroxytryptamine on feeding in rats. *Ann. N.Y. Acad. Sci.* **305:** 590–594.

Hollister A. S., Ervin G. N., Cooper B. R. and Breese G. (1975) The roles of monoamine neural systems in the anorexia induced by (+)-amphetamine and related compounds. *Neuropharmacology* **14:** 715–723.

Ishizaki F. (1974) Goldthioglucose-induced lesions and quantitative changes of monoamines in the rat brain. *Yonago Acta Medica* **18:** 1–8.

Jesperson S. and Scheel-Kruger J. (1970) Antagonism by methysergide of 5-hydroxytryptamine-like action of toxic doses of fenfluramine in dogs. *J. Pharmac.* **22:** 637–638.

Jesperson S. and Scheel-Kruger J. (1973) Evidence for a difference in mechanism of action between fenfluramine- and amphetamine-induced anorexia. *J. Pharm. Pharmac.* **25:** 49–54.

Joyce D. and Mrosovsky N. (1964) Eating, drinking and activity in rats following 5-hydroxytryptophan (5-HTP) administration. *Psychopharmacologia* **5:** 417–423.

Kantak K. M., Wayner M. J. and Stein J. M. (1978) Effects of various periods of food deprivation on serotonin synthesis in the lateral hypothalamus. *Pharmac. Biochem. Behav.* **9:** 535–541.

Latham C. J. and Blundell J. E. (1979) Evidence for the effect of tryptophan on the pattern of food consumption in free feeding and food deprived rats. *Life Sci.* **24:** 1971–1978.

Leibowitz S. F. and Papadakos P. J. (1978) Serotonin–norepinephrine interactions in the paraventricular nucleus: antagonistic effects on feeding behaviour in the rat. *Neurosci. Abstr.* **4:** 452.

Leibowitz S. F. (1980) Neurochemical systems of the hypothalamus—control of feeding and drinking behaviour and water-electrolyte excretion. In: *Handbook of the Hypothalamus* (Morgane P. J. and Panksepp J., Eds), pp. 299–347. Marcell Dekker, New York.

MacKenzie R. C., Hoebel B. G., Ducret R. P. and Trulson M. E. (1979) Hyperphagia following intraventricular *p*-chlorophenylalanine- leucine- or tryptophan-methyl esters: lack of correlation with whole brain serotonin levels. *Pharmac. Biochem. Behav.* **10:** 951–955.

Marshall J. F., Richardson J. S. and Teitelbaum P. (1974) Nigrostriatal bundle damage and the lateral hypothalamic syndrome. *J. comp. Physiol. Psychol.* **87:** 800–830.

McArthur R. A. and Blundell J. E. (1982) Effects of age and feeding regime on self selection of protein and carbohydrate. *Appetite* **3:** 153–162.

McDermott L. J., Alheid G. F., Halaris A. E. and Gross man S. D. (1977) A correlation analysis of the effects of surgical transections of three components of the MFB on ingestion behaviour and hypothalamic, striatal and telencephalic amine concentrations. *Pharmac. Biochem. Behav.* **6:** 203–214.

Nobin A. and Bjorklund A. (1978) Degenerative effects of various neurotoxic indoleamines on central monoamine neurons. *Ann. N.Y. Acad. Sci.* **305:** 305–327.

Orthen-Gambill N. and Kanarek R. B. (1982) Differential effects of amphetamine and fenfluramine on dietary self-selection in rats. *Pharmac. Biochem. Behav.* **16:** 303–309.

Perez-Cruet J., Tagliamonte A., Tagliamonte P. and Gessa G. L. (1972) Changes in brain serotonin metabolism associated with fasting and satiation in rats. *Life Sci.* **11:** 31–39.

Peters J. C., Bellissimo D. B. and Harper A. E. (1984)

L-Tryptophan injection fails to alter nutrient selection by rats. *Physiol. Behav.* **32:** 253–259.

Pollock J. D. and Rowland N. (1981) Peripherally administered serotonin decreases food intake in rats. *Pharmac. Biochem. Behav.* **15:** 179–183.

Russell G. F. M. (1979) Bulimia Nervosa: an ominous variant of anorexia nervosa. *Br. J. Psychiat.* **9:** 429–3448.

Saller C. F. and Stricker E. M. (1976) Hyperphagia and obesity in rats after intraventricular injection of 5,7-dihydroxytryptamine. *Science* **192:** 384–386.

Samanin R., Ghezzi D., Valzelli L. and Garattini S. (1972) The effects of selective lesioning of brain serotonin or catecholamine containing neurones on the anorectic activity of fenfluramine and amphetamine. *Eur. J. Pharmac.* **19:** 318–322.

Silverstone T. and Schuyler D. (1975) The effect of cyproheptadine on hunger, calorie intake and body weight in man. *Psychopharmacologia* **40:** 335–340.

Simansky K. J., Bourbonais K. A. and Smith G. P. (1982) Abdominal vagotomy reduces the dipsogenic but not the anorexic action of systemic serotonin in rats. *Neurosci. Abstr.* **8:** 605.

Singer G., Sanghvi I. and Gershon S. (1971) Exploration of certain behavioural patterns induced by psychoactive agents in the rat. *Commun. Behav. Biol.* **6:** 307–314.

Speight L. and Avery G. (1972) Pizotofen (BC-105): a review of its pharmacological properties and its therapeutic efficacy in vascular headaches. *Drugs* **3:** 159.

Sugrue M. F., Goodlet I. and McIndewar I. (1975) Failure of depletion of rat brain 5-hydroxytryptamine to alter fenfluramine-induced anorexia. *J. Pharm. Pharmac.* **27:** 950–953.

Tedeschi D. H. (1966) Pharmacological evaluation of anorectic drugs. In: *Methods in Drug Evaluation* (Mantegazza P. and Piccinini R., Eds), pp. 341–350. North Holland, Amsterdam.

Trulson M. E., Eubanks E. E. and Jacobs B. L. (1976) Behavioural evidence for supersensitivity following destruction of central serotonergic nerve terminals by 5,7-dihydroxytryptamine. *J. Pharmac. exp. Ther.* **198:** 23–32.

Ungerstedt U. (1971) Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigrostriatal dopamine system. *Acta physiol. scand.* **367:** 95–122.

Waldbillig R. J., Bartness T. J. and Stanley B. G. (1981) Increased food intake, body weight, and adiposity in rats after regional neurochemical depletion of serotonin. *J. comp. Physiol. Psychol.* **95:** 391–405.

Weinberger S. B., Knapp S. and Mandell A. J. (1978) Failure of tryptophan load-induced increases in brain serotonin to alter food intake in the rat. *Life Sci.* **22:** 1595–1602.

Wurtman J. J. and Wurtman R. J. (1977) Fenfluramine and fluoxetine spare protein consumption while suppressing caloric intake by rats. *Science* **198:** 1178–1180.

Wurtman J. J. and Wurtman R. J. (1979) Drugs that enhance central serotonergic transmission diminish elective carbohydrate consumption by rats. *Life Sci.* **24:** 895–904.

Wurtman R. J., Heftl F. and Melamed E. (1981) Precursor control of neurotransmitter synthesis. *Pharmac. Rev.* **32:** 315–335.